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(54) **Title:** A PROCESS FOR THE PREPARATION OF FLUDARABINE PHOSPHATE FROM 2-FLUOROADENINE AND FLUDARABINE PHOSPHATE SALTS WITH AMINES OR AMMONIA

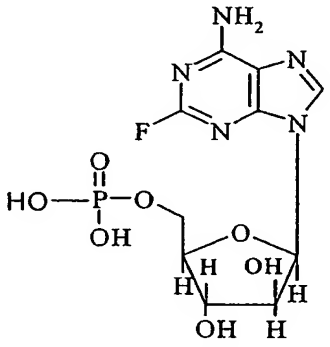
(57) **Abstract:** The invention provides a process for the preparation of fludarabine phosphate from 2-fluoroadenine and 9-β-D-arabinofuranosyl-uracil using *Enterobacter aerogenes* (EBA). 2-Fluoroadenine is reacted with 9-β-D-arabinosyl-uracile in a water solution at pH = 7 in the presence of EBA cell paste, to yield fludarabine. Fludarabine is then treated with acetic anhydride and the resulting acetylderivative is crystallised and hydrolysed to fludarabine. Phosphorylation and purification with organic amines or with ammonium hydroxide afford fludarabine phosphate.

WO 2004/087939 A1

A PROCESS FOR THE PREPARATION OF FLUDARABINE PHOSPHATE FROM 2-FLUOROADENINE AND FLUDARABINE PHOSPHATE SALTS WITH AMINES OR AMMONIA

FIELD OF THE INVENTION

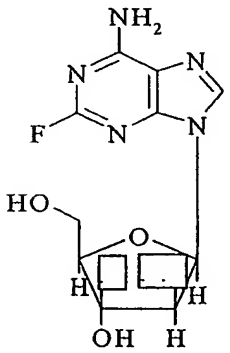
The present invention relates to a process for the preparation of fludarabine phosphate (**I**), in particular to a process for the preparation of fludarabine phosphate from 2-fluoroadenine and 9-β-D-arabinofuranosyl-uracil using *Enterobacter aerogenes*.



(I)

TECHNOLOGICAL BACKGROUND

Fludarabine (9-β-D-arabinofuranosyl-2-fluoroadenine) (**II**) is a purine nucleoside antimetabolite resistant to adenosine deaminase, employed for the treatment of leukemia.



(II)

Fludarabine is usually administered as a pro-drug, fludarabine phosphate, which is also the natural metabolite. Fludarabine was firstly

synthesised by Montgomery (**US 4,188,378** and **US 4,210,745**) starting from 2-aminoadenine. The method comprised acetylation of 2-aminoadenine, reaction with a benzyl-protected chlorosugar, deacetylation of the amino groups, diazotization and fluorination of the 2-amino group followed by deprotection of the sugar residue.

Fludarabine phosphate can be obtained according to conventional phosphorylation methods, typically by treatment with trimethylphosphate and phosphoryl chloride. Recently, a method for preparing highly pure fludarabine, fludarabine phosphate and salts thereof has been disclosed by Tilstam et al. (**US 6,046,322**).

Enzymatic synthesis has been regarded as a valid alternative to conventional methods for the synthesis of nucleosides and nucleotides derivatives. **EP 0 867 516** discloses a method for the preparation of sugar nucleotides from sugar 1-phosphates and nucleosides monophosphates by use of yeast cells having nucleoside diphosphate-sugar pyrophosphorylase activity. **EP 0 721 511 B1** discloses the synthesis of vidarabine phosphate and fludarabine phosphate by reacting an arabinonucleotide with an arylphosphate in the presence of a microorganism able to catalyse the phosphorylation of nucleosides. This method is particularly convenient in that it does not require purified enzymes, but it does not allow to synthesise vidarabine and fludarabine.

DESCRIPTION OF THE INVENTION

It has now been found that fludarabine can be conveniently prepared by reacting 2-fluoroadenine with 9-β-D-arabinofuranosyl-uracil (Ara-U) in the presence of *Enterobacter aerogenes* (EBA).

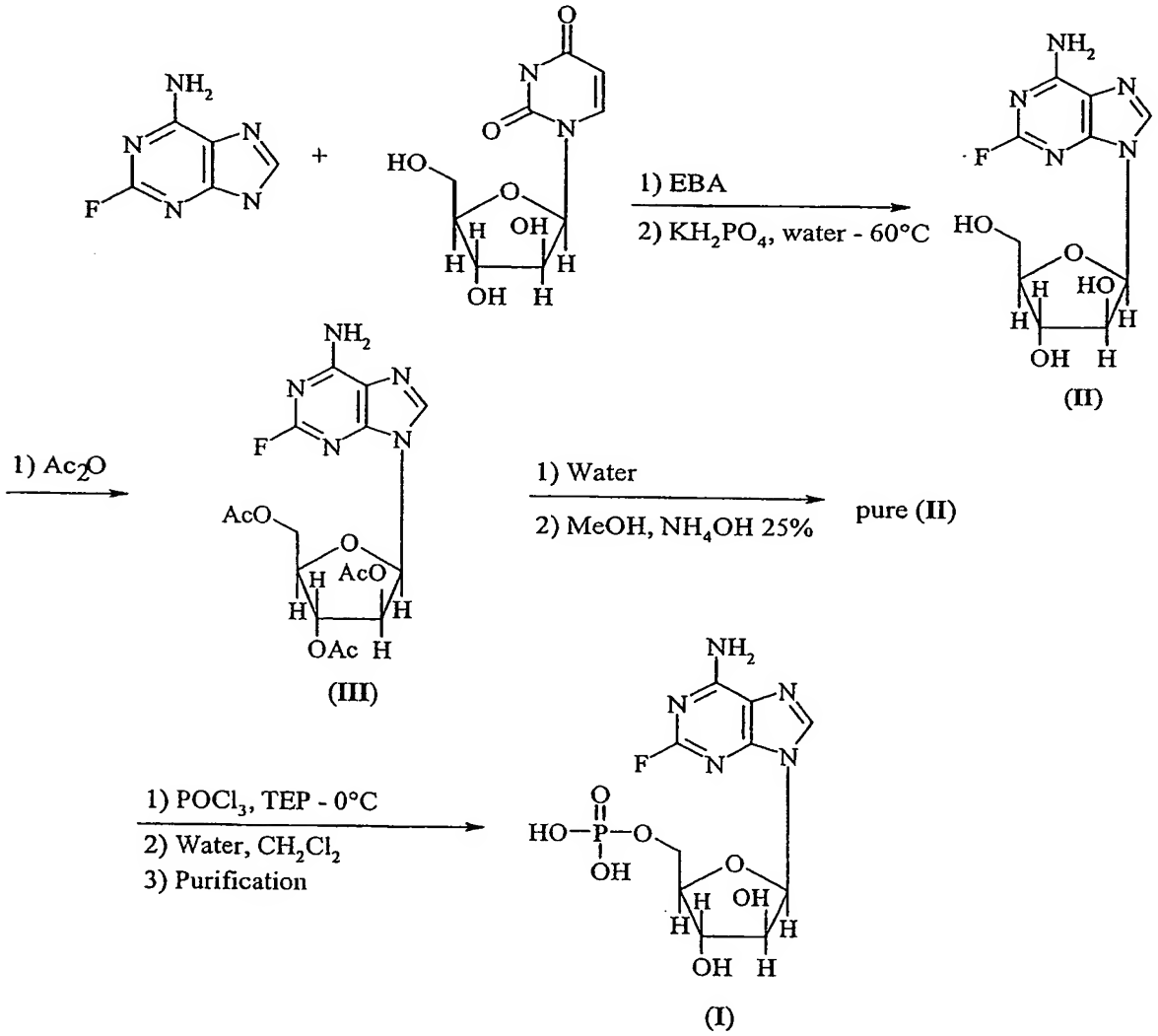
The present invention relates to a process for the preparation of fludarabine phosphate (**I**) illustrated in the scheme and comprising the following steps:

a) reaction of 2-fluoroadenine with 9-β-D-arabinofuranosyl-uracil in the presence of *Enterobacter aerogenes* to give crude fludarabine (**II**);

b) treatment of crude fludarabine with acetic anhydride to 2',3',5'-tri-O-acetyl-9-β-D-arabinofuranosyl-2-fluoroadenine (**III**);

c) hydrolysis and recrystallisation of intermediate (**III**) to give pure fludarabine;

d) phosphorylation of fludarabine to give fludarabine phosphate (**I**).



Step a) is carried out in a 0.03 - 0.05 M KH_2PO_4 solution, heated to a temperature comprised between 50 and 70°C, preferably to 60°C, adjusted to

pH 7 with KOH pellets and added with 2-fluoroadenine, Ara-U and EBA. The concentration of 2-fluoroadenine in the solution ranges from 0.02 to 0.03 M, while 9-β-D-arabinofuranosyl-uracil is used in a strong excess; preferably, the molar ratio between 9-β-D-arabinofuranosyl-uracil and 2-fluoroadenine ranges from 5:1 to 7:1; more preferably from 5.5:1 to 6.5:1. 2 - 2.5 l of cell culture per l of KH_2PO_4 solution is used. The mixture is stirred at 60°C, adjusting the pH to 7 with a 25% KOH solution and the reaction is monitored by HPLC. Once the reaction is complete (about 24 - 26 hours), the cell material is separated by conventional dialysis and the permeated solutions are recovered and kept cool overnight. Crystallised fludarabine contains 10% 9-β-D-arabinofuranosyl adenine, which can be conveniently removed by means of steps b) and c).

In step b) crude fludarabine from step a) is dissolved in 9 - 11 volumes of acetic anhydride, preferably 10 volumes and reacted at 90 - 100°C under stirring, until completion of the reaction (about 10 - 12 h). Acetic anhydride is co-evaporated with acetone and the product is suspended in water.

The hydrolysis of step c) is carried out with methanol and ammonium hydroxide. Typically, compound (**III**) from step b) is suspended in 9 - 11 volumes of methanol and 2.5 - 3.5 volumes of 25% NH_4OH and stirred at room temperature until complete hydrolysis (about 20 hours; the completion of the reaction can be promoted by mildly warming up the mixture to 30 - 32°C). Fludarabine precipitates by cooling the mixture to 10°C and is further hot-crystallised with water, preferably with 50 - 70 ml of water per gram of fludarabine or with a water/ethanol mixture (1/1 v/v) using 30 - 40 ml of mixture per gram of fludarabine. Fludarabine is recovered as the monohydrate and has a HPLC purity higher than 99%.

Even though the conversion of fludarabine into fludarabine phosphate (step d) can be carried out according to any conventional technique, for example as disclosed in US 4,357,324, we have found that an accurate control of the reaction

temperature significantly improves the yield. According to a preferred embodiment of the invention, the reaction between phosphorous oxychloride, triethylphosphate and fludarabine is carried out at -10°C, and fludarabine phosphate is precipitated from water at 0°C. We have also surprisingly found that phosphorilation of fludarabine with a moderate water content, i.e. up to 5 - 6%, remarkably reduces the formation of diphosphate derivates.

Fludarabine phosphate can be further purified by salification with organic amines or with NH_4OH. An aqueous or aqueous-organic solution of fludarabine phosphate is treated with an equimolar amount of amine, preferably selected from the group consisting of triethylamine, diisopropylamine, benzylamine, tributylamine, dibenzylamine and dicyclohexylamine or with NH_4OH, typically 25% NH_4OH, and the resulting salt is submitted to acidic hydrolysis with a diluted acid, preferably with diluted 3 - 5% HCl. Suitable organic solvents are water-miscible organic solvents. Before hydrolysis, the fludarabine phosphate salt can be submitted to cation-exchange reaction with NH_4Cl to obtain an ammonium salt which is subsequently hydrolysed. This procedure is particularly advantageous when fludarabine phosphate is salified with dicyclohexylamine. Purification of fludarabine phosphate by treatment with organic amines or with NH_4OH allows to obtain a final product with a purity that meets Pharmacopoeia specifications.

The salts of fludarabine phosphate with organic amines or with ammonia are new and are a further object of the invention. Particularly preferred is the dicyclohexylammonium salt.

In summary, the present invention allows to obtain the following advantages: fludarabine is prepared by enzymatic synthesis without the use of pure enzymes and is therefore particularly suitable for industrial scale; fludarabine is easily recovered and purified from 9-β-D-arabinofuranosyl adenine by acetylation without the need of chromatographic purification, since

the triacetyl-derivative precipitates from water with high purity and yield; fludarabine phosphate can be obtained in high yield and purity from fludarabine with a water content of 5 - 6% by controlling the reaction temperature in the phosphorylation step; finally, the purification of fludarabine phosphate by salification with an organic amine or NH_4OH, allows to minimise product decomposition (i.e formation of impurities A and B that occurs when fludarabine phosphate is crystallised at high temperature).

The following examples illustrate the invention in more detail.

EXAMPLES

Example 1 - Crude 9-β-D-arabinofuranosyl-2-fluoroadenine (II)

A solution of KH_2PO_4 (123 g, 0.9 moles) in water (13 l) was heated to 60°C under stirring and the pH adjusted to 7 with KOH pellets (130 g, 2.32 moles), then added with Ara-U (1451 g, 5.94 moles), 2-fluoroadenine (150 g, 0.98 moles) and EBA (ATCC® n° 13048) cell culture (30 l).

The mixture was stirred at 60°C for 24 - 26 hours, adjusting the pH to 7 with a 25% KOH solution and monitoring the reaction by HPLC.

After 24 - 26 hours the cell material was separated by dialysis at 50° - 55°C, diluting the mixture with water. The permeated yellow clear solutions were collected, pooled (50 l) and left to stand at 0° - 5°C overnight. The resulting crystalline precipitate was filtered and washed with cold water (2 l).

The product was dried at 45°C under vacuum for 16 hours to give 110 g of the crude compound (II) which was shown by HPLC to be a mixture of (I) (90%) and 9-β-D-arabinofuranosyl adenine (10%).

Example 2 - Pure 9-β-D-arabinofuranosyl-2-fluoroadenine (II)

9-β-D-arabinofuranosyl-2-fluoroadenine (II) (30 g, 0.095 moles) was suspended in acetic anhydride (300 ml) and heated to 95°C under stirring.

After 7 hours a clear solution was obtained and left to react at 95°C for

further 2 - 3 hours until the acetylation was completed.

The resulting yellow solution was then concentrated under vacuum at 45°C and the residue was co-evaporated with acetone (2 x 50 ml) and suspended in water (600 ml). The water suspension was cooled to room temperature and left under stirring for 1 hour.

The product was collected by filtration and washed with water (2 x 100 ml) to give 34 g of wet 2',3',5'-tri-O-acetyl-9-β-D-arabinofuranosyl-2-fluoroadenine (**III**).

Wet compound (**III**) was suspended in methanol (300 ml) and added with 25% NH_4OH (100 ml). The mixture was left to stand at room temperature overnight and after 19 hours was warmed to 30° - 32°C for 3 hours, until no starting material was detected by HPLC.

The suspension was cooled to 10°C for 1 hour, then the product was collected by filtration and washed with a methanol-water mixture (2 x 25 ml, 3:1 v/v). The product was dried under vacuum overnight to give 17.5 g of fludarabine (**II**) (98.4% HPLC purity).

Method A

Re-crystallisation of compound (**II**) (17.5 g, 0.061 moles) was also carried out by suspending the product in water (875 ml) and heating to 95°C until a clear solution was obtained. The solution was allowed to cool spontaneously to room temperature and the crystalline product was filtered, washed with cold water (2 x 50 ml) and dried under vacuum overnight, to give 15.5 g of pure fludarabine (**II**) (99.3% HPLC purity).

Method B

Fludarabine (II) (35 g, 0.123 moles) was also re-crystallized by suspending the product in a water/ethanol mixture (1/1, v/v) (1050 ml) and heating to 80°C until a clear solution was obtained. The solution was allowed to cool spontaneously to room temperature and the crystalline product was filtered,

washed with a water/ethanol mixture (2 x 50 ml) and dried under vacuum overnight, to give 32 g of pure fludarabine (II) (99% HPLC purity).

Example 3 - 9-β-D-arabinofuranosyl-2-fluoroadenine-5'-phosphate (I)

Method A

Phosphorous oxychloride (5 g, 3 ml, 0.033 mol) was added to cold (-10°C) triethylphosphate (50 ml) and the solution was kept at -10°C for 1 hour, thereafter fludarabine (II) (5 g, 0.018 mol) was added with stirring at -10°C.

After about 6 hours the reaction mixture turned light-yellow and became homogeneous. The mixture was kept at -10°C overnight and after 23 hours the phosphorylation was completed. After addition of 40 ml of cold water (2°C) the solution was stirred for 1 hour at 0°C and extracted with cold (0°C) methylene chloride (100 ml, two 50 ml portions).

The aqueous solution was kept under vacuum at room temperature for 1 hour and allowed to stand at 0°C for 24 hours. The resulting crystalline product (I) was collected by filtration and washed with ethanol (2 x 20 ml).

The product was dried at 40°C under vacuum for 24 hours (yield: 5 g). If desired, drying can be omitted and crude fludarabine phosphate can be directly submitted to purification.

Method B

Phosphorous oxychloride (10.7 g, 6.4 ml, 0.07 mol) was added to cold (-10°C) triethylphosphate (50 ml) and the solution was kept at -10°C for 1 hour, thereafter fludarabine (II) with a water content of 5 - 6% (5 g, 0.018 mol) was added with stirring at -10°C.

After about 2 - 3 hours the reaction mixture turned light-yellow and became homogeneous. The mixture was kept at -10°C overnight until the phosphorylation was completed. After addition of 40 ml of cold water (2°C) the solution was stirred for 1 hour at 0°C and extracted with cold (0°C) methylene chloride (3 x 50 ml).

The aqueous solution was kept under vacuum at room temperature for 1 hour and allowed to stand at 0 - 5°C for 1 - 2 hours. The resulting crystalline product (I) was collected by filtration and washed with cold water (3 x 10 ml).

The product was dried at 40°C under vacuum for 24 hours (yield: 4.2 g). If desired, drying can be omitted and crude fludarabine phosphate can be directly submitted to purification.

Example 4 - Purification of fludarabine phosphate with organic amines and NH_4OH

Method A - crystallization with triethylamine, diisopropylamine, benzylamine, tributylamine, dibenzylamine and NH_4OH

Fludarabine phosphate (5 g - 0.014 mol) was suspended in water (40 - 50 ml) at room temperature and the amine (1 - 1.1 eq) or 25% NH_4OH was added dropwise until a clear solution was obtained (pH = 4.9 - 5.6). The solution was added dropwise to a dilute solution of hydrochloric acid (3 - 5%) at room temperature to obtain a precipitate. The suspension was stirred at 0° - 5°C for 1 - 2 hours and the pH was adjusted to 1.9 - 2.1 with a solution of hydrochloric acid (10 - 15%). The precipitate was collected by filtration, washed with cold water (10 - 20 ml) and dried at 50° - 60°C under vacuum for 24 hours.

The results are reported in the following table:

Base	HPLC Purity (%)	Yield (%)
Triethylamine	99.3	75
Diisopropylamine	99.3	50
Benzylamine	98.9	46
Tributylamine	99.2	53
Dibenzylamine	99.4	47
25%NH_4OH	99.5	70

Method B - Crystallization with dicyclohexylamine:

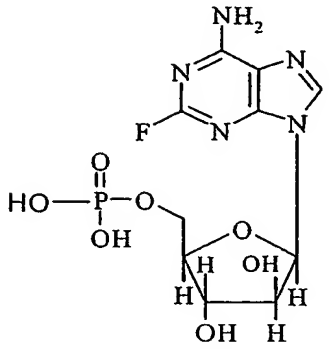
Fludarabine phosphate (3 g - 0.008 mol) was suspended in water (4 - 6 ml)

and acetone (10 - 12 ml) at room temperature. Then, dicyclohexylamine (1 - 1.2 eq) was added dropwise under stirring until a clear solution was obtained (2 - 3 hours; pH = 6.5 - 7). After further 15 - 30 minutes a precipitate was obtained and the mixture was stirred at room temperature for 1 hour. Fludarabine phosphate dicyclohexylammonium salt was collected by filtration and washed with acetone (3 - 6 ml).

The wet product was suspended in 5% aqueous NH_4Cl (60 - 80 ml) at room temperature, for 2 - 3 hours. Then, dicyclohexylammonium chloride was collected by filtration and the solution of fludarabine phosphate ammonium salt was added dropwise to a dilute solution of hydrochloric acid (3 - 5%) at room temperature to obtain a precipitate. The suspension was stirred at 0° - 5°C for 1 - 2 hours and the pH was adjusted to 1.9 - 2.1 with aqueous hydrochloric acid (10 - 15%). The precipitate was collected by filtration and washed with cold water (10 - 20 ml). The product was dried under vacuum for 24 hours to give 2.1 g of fludarabine phosphate (99. 4% HPLC purity).

CLAIMS

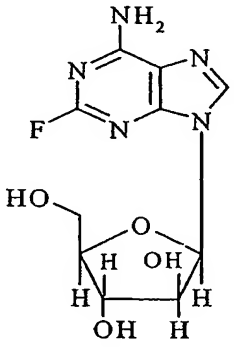
1. A process for the preparation of fludarabine phosphate (I)



(I)

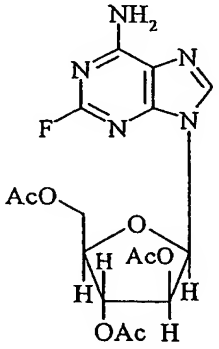
comprising the following steps:

a) reaction of 2-fluoroadenine with 9-β-D-arabinofuranosyl-uracil in the presence of *Enterobacter aerogenes* to give crude fludarabine (II);



(II)

b) treatment of crude fludarabine with acetic anhydride to give 2',3',5'-tri-O-acetyl-9-β-D-arabinofuranosyl-2-fluoroadenine (III);



(III)

c) hydrolysis and recrystallisation of compound (**III**) to give pure fludarabine (**II**);

d) phosphorylation of fludarabine to give fludarabine phosphate (**I**).

2. A process according to claim 1 wherein step a) is carried out at a temperature comprised between 50 and 70°C, and the molar ratio between 9-β-D-arabinofuranosyl-uracil and 2-fluoroadenine ranges from 5:1 to 7:1.

3. A process according to claim 1 or 2 wherein crude fludarabine from step a) is recovered by dialysis.

4. A process according to anyone of claims 1 - 3 wherein step b) is carried out by dissolving crude fludarabine in 9 - 11 volumes of acetic anhydride at 90 - 100°C.

5. A process according to any one of claims 1 - 4 wherein intermediate (**III**) from step b) is hydrolysed with methanol and ammonium hydroxide.

6. A process according to any one of claims 1 - 5 wherein fludarabine obtained from step c) is hot-crystallised from water or from a water/ethanol mixture.

7. A process according to any one of claims 1 - 6 wherein the phosphorylation reaction of step d) is carried out at -10°C and the resulting fludarabine phosphate is precipitated from water at 0°C.

8. A process according to any one of claims 1 - 7 wherein fludarabine phosphate is purified by treatment with an organic amine or NH_4OH followed by acidic hydrolysis.

9. A process according to claim 8 wherein the organic amine is selected from the group consisting of triethylamine, diisopropylamine, benzylamine, tributylamine, dibenzylamine and dicyclohexylamine.

10. Fludarabine phosphate salts with organic amines or with ammonia.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/001239

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12P19/32 C12P19/40 C07H19/16 C07H19/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12P C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 602 246 A (BAUMAN JOHN G ET AL) 11 February 1997 (1997-02-11) column 1, line 60 - line 65 column 6, line 7 - line 21 column 18, line 21 - line 23 abstract	1-7
Y	GB 2 006 185 A (AJINOMOTO KK) 2 May 1979 (1979-05-02) claims 1,8,10; examples 2,6	1-7
Y	WO 95/09244 A (SCHERING AG ;HUMMEL MARQUARDT HEIDI (DE); SCHMITZ THOMAS (DE); KEN) 6 April 1995 (1995-04-06) cited in the application abstract	1-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2004	04/08/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 376 518 A (LILLY CO ELI) 4 July 1990 (1990-07-04) cited in the application the whole document	8-10
Y	US 6 046 322 A (TILSTAM ULF ET AL) 4 April 2000 (2000-04-04) page 6, lines 13-21; claim 8	8-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/001239

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5602246	A	11-02-1997	AT	162197 T	15-01-1998
			AU	676874 B2	27-03-1997
			AU	5679294 A	22-06-1994
			CA	2149117 A1	09-06-1994
			DE	69316391 D1	19-02-1998
			DE	69316391 T2	13-08-1998
			DK	670845 T3	14-09-1998
			EP	0670845 A1	13-09-1995
			ES	2114173 T3	16-05-1998
			GR	3026499 T3	31-07-1998
			JP	8505608 T	18-06-1996
			JP	3523870 B2	26-04-2004
			WO	9412514 A1	09-06-1994
			US	5668270 A	16-09-1997
GB 2006185	A	02-05-1979	JP	1407628 C	27-10-1987
			JP	54095793 A	28-07-1979
			JP	62014277 B	01-04-1987
			JP	1337679 C	29-09-1986
			JP	54032695 A	10-03-1979
			JP	61003480 B	01-02-1986
			JP	1471120 C	14-12-1988
			JP	54092695 A	23-07-1979
			JP	63015279 B	04-04-1988
			CA	1120876 A1	30-03-1982
			DE	2835151 A1	22-02-1979
			FR	2400033 A1	09-03-1979
			NL	7808321 A	13-02-1979
			US	4371613 A	01-02-1983
WO 9509244	A	06-04-1995	AT	197720 T	15-12-2000
			CA	2172817 A1	06-04-1995
			DE	59409594 D1	28-12-2000
			DK	721511 T3	05-03-2001
			WO	9509244 A1	06-04-1995
			EP	0721511 A1	17-07-1996
			ES	2153859 T3	16-03-2001
			GR	3035445 T3	31-05-2001
			JP	9502881 T	25-03-1997
			PT	721511 T	31-05-2001
			US	5700666 A	23-12-1997
EP 0376518	A	04-07-1990	CA	2004695 A1	12-06-1990
			DE	68924970 D1	11-01-1996
			DE	68924970 T2	15-05-1996
			EP	0376518 A1	04-07-1990
			ES	2081308 T3	01-03-1996
			JP	2202896 A	10-08-1990
			JP	2817972 B2	30-10-1998
US 6046322	A	04-04-2000	AT	231880 T	15-02-2003
			AU	739574 B2	18-10-2001
			AU	2155099 A	28-06-1999
			CA	2313486 A1	17-06-1999
			DE	59807096 D1	06-03-2003
			DK	1047704 T3	23-06-2003
			WO	9929710 A2	17-06-1999
			EP	1047704 A2	02-11-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/001239

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6046322 A		ES 2190136 T3	16-07-2003
		HK 1033831 A1	05-09-2003
		HU 0100169 A2	28-11-2001
		JP 2001525418 T	11-12-2001
		NO 20002962 A	09-06-2000
		PL 341659 A1	23-04-2001
		SI 1047704 T1	29-02-2004
		SK 8872000 A3	12-03-2001
		TW 424093 B	01-03-2001
		ZA 9811338 A	10-06-1999